



February 23, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Rockville, MD 20857

GlaxoSmithKline
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Re: Docket No. 2004N-0535 Notice: Agency Information Collection Activities; Proposed Collection; Comment Request; MedWatch: FDA Medical Products Reporting Program; 69 Federal Register 77256; December 27, 2004

Dear Sir/Madam:

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products, vaccines, and over-the-counter devices. We are actively involved, on a daily basis, in the collection, review, follow-up, and reporting of adverse events, and have a long-standing and vital interest in post-marketing adverse event collection, reporting, and evaluation. We appreciate the opportunity to provide comments on the proposed revisions to the Form FDA 3500 and Form FDA 3500A (MedWatch forms).

We have some concerns regarding the proposed changes to the Form FDA 3500A. Our major concerns include:

- Addition of new data fields introduces divergence from international data standards for individual case safety reports.
- Some of the new fields appear to require submission of information not required by current FDA regulations and/or guidelines.
- There are a number of seemingly minor formatting changes to existing fields, which will require considerable expense and effort to implement, with no apparent benefit to FDA, public health, or industry.

Detailed comments relating to these points are outlined below, followed by comments on the four points for which the Agency specifically requested comments in the Federal Register notice.

General Comments on Proposed Changes to Form FDA 3500A (mandatory form):

1. Some of the new information proposed to be collected is not consistent with internationally agreed data elements for post-marketing adverse event reports, and is not part of the ICH guideline on Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), nor the ICH Data Elements for the Transmission of Individual Case Safety Reports (E2B). Examples include: product use errors and product switches as types of reports (section B.1), "no harm" as an outcome (section B.2), and product availability information (section C). Addition of these fields to the Form FDA 3500A will introduce inconsistency in the information that applicants report to FDA, depending on the reporting format used (e.g., paper vs electronic submission). There would also be a discrepancy in the information provided to FDA vs that provided to other regulatory authorities, as CIOMS forms and the ICH E2B data standards do not include these fields.

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2. Although the Federal Register notice states that the proposed modifications to the forms "...reflect changes that will bring the form into conformation with current regulations, rules, and guidances...", we are concerned that the proposed additions of information included in the Form FDA 3500A go above and beyond the current regulations and guidance for post-marketing reporting of adverse events in association with marketed drug and biologic products. For example, there is currently no requirement for submission of medication error reports that do not involve an adverse event. Although FDA has proposed medication error reporting in the March 2003 proposed rule on safety reporting for drug and biologic products, and in the 2001 draft guidance document, neither of these documents have been finalized. It is possible that some of the new information may be required for medical device reports (e.g., information regarding availability of the product for evaluation); however, placement of these fields in the general section of the form implies that it is mandatory for all reports. Clarification from FDA in the form of accompanying instructions for completing the form should be provided for comment in conjunction with the proposed revised Form FDA 3500A.

As part of the ongoing dialog between FDA and individual companies regarding the safety profile of their products, a particular concern relating to issues such as medication errors or product quality with a specific product could be addressed by prospective collection of additional data by the responsible company. Such a targeted approach for specific products with potential areas of concern appears to be a more focused way of addressing a safety concern in these areas.

3. GSK currently submits the vast majority of our expedited and periodic post-marketing adverse event reports to FDA electronically, and most of the major pharmaceutical companies are moving in this direction. Given that FDA has consistently advocated for electronic submission in place of paper forms, we find it odd that the Agency is now contemplating revision of a form that is quickly becoming obsolete. In fact, at a recent PhRMA meeting, an FDA representative noted that FDA currently receives approximately 35% of expedited reports electronically, and is moving ahead with a proposed rule to require electronic submission of expedited reports in 2005. A number of pharmaceutical companies, including GSK, have been working with FDA on electronic submission of Periodic (non-expedited) individual case safety reports, and GSK has been doing this for over a year. We suggest that the Agency's and industry's resources would be more effectively utilized if they were directed toward enhancing electronic submissions, rather than revising the Form FDA 3500A.
4. Most pharmaceutical companies that still submit reports using the mandatory paper Form FDA 3500A submit reports to FDA using computer-generated facsimiles of the form. GSK currently submits computer-generated paper Forms FDA 3500A only as a back-up to prevent late expedited reports in rare instances of server or network outages, and for a relatively small number of cases that include attachments (e.g., literature) or for which the Agency does not yet accept electronic submissions (e.g., voluntary dietary supplement reports). It will require considerable resource and effort (reprogramming and re-validation) to reformat information already contained in the existing Form FDA 3500A to comply with the revised form, with essentially no benefit to FDA, the public health, or GSK.

For example, there is no change to the information required for Section A, Patient Information; only the spacing and format of the information has changed. Similarly, in the revised Section D, Suspect Product(s), information regarding dose, frequency and route must be output into specific boxes; this information is currently provided on a single line. Although these appear to be very minor changes, the remapping of data fields, reprogramming, and revalidation of computer-generated forms will require significant resource. Additionally, the new boxes in Section B5 related to use during pregnancy and lactation appear to duplicate information that is usually provided via adverse event (MedDRA) terms, as well as in the narrative text. We fail to see the

need for including the same information in multiple places in the report, especially as space is at a premium.

We suggest that reformatting of existing information blocks be eliminated. We also urge that if the Agency does add these new fields to the Form FDA 3500A, that they grant waivers to companies such as GSK that submit their reports electronically, and use paper forms only when electronic submission is not possible.

5. We also have questions regarding placement of section I, All Manufacturers. Currently, pharmaceutical manufacturers can replace the Suspect Medical Device box on the front of the Form FDA 3500A with the All Manufacturers box, so that the form is one page. With the current form, this places the All Manufacturers box just before the Initial Reporter information, a logical placement. However, with the proposed revised form, the Other/Concomitant Medical Products block is between the Suspect Medical Device block and the Initial Reporter information. Does FDA intend for the All Manufacturers information to continue to replace the Suspect Medical Device information when the form is modified for pharmaceutical product use, or should it continue to be placed immediately before the Initial Reporter information?
6. Consistent with the comments above, we recommend that FDA update the instructions for completing the Form FDA 3500A, and issue them in conjunction with the final revised form, so that we have a clear understanding of the required information in order to appropriately modify our procedures and databases to capture this information, and reprogram and revalidate our systems to output the required information.

Without these instructions, it is difficult to discern which fields pertain to all products, and which apply to only drugs or only medical devices, or apply only to certain types of reports. The revised form also introduces several new concepts that require clarification, particularly the categories of "product switch" and "product use error" in section B1, and "no harm" in section B2. Although our comments are focused on the mandatory reporting form, we note that the proposed voluntary Form FDA 3500 states "see instructions" next to the "Product switch" category, yet the instructions printed on the back of the form make no mention of this item. We also note that the instruction to include information "if known" that currently appears in some fields has been eliminated, raising the question of whether these data elements are now considered mandatory. Examples of these fields include strength and manufacturer name, lot number, and expiration date (section D).

Instructions are also needed to clarify whether certain fields that are currently required only for medical devices or product problems (e.g., whether product is available for evaluation, NDC number) are required for all reports, or only certain types of reports. The questions regarding whether the Agency considers return of product for evaluation to be required in every instance are of particular concern, as this would appear to go beyond current regulations and guidelines, and would have significant impact on the working practices of our safety department (in terms of obtaining returned product), as well as our Quality Assurance department (in storing and analyzing returned products). The Agency's expectations regarding submission of results of any evaluation or analysis as follow-up reports also need to be clarified. The value of obtaining and analyzing returned product for every adverse event report is questionable, and this should be required only when evaluation of the product would provide insight into the etiology of the adverse event.

7. Because we will not be able to initiate any changes to our databases or computer-generated Form FDA 3500A until the revised form is finalized and the updated instructions are issued, we recommend that FDA allow at least six months for implementation of the revised form after it is finalized and made available to the public.

Specific Comments on the Questions Posed in the Federal Register Notice

1. *Comment on whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility*

GSK believes that collection of information relating to adverse events is necessary for the proper performance of FDA's functions. Use of standard forms such as the FDA 3500 and FDA 3500A facilitate the collection and reporting of adverse event information. However, as noted above, we believe that the proposed changes to the Form FDA 3500A are not necessary, do not reflect current regulations or guidelines for reporting of adverse events in association with marketed drug and biologic products, and will require considerable effort to implement, with no obvious benefit to public health. Although some of the proposed changes are envisioned in the March 2003 proposed rule on safety reporting for drug and biologic products, information from FDA indicates that it is highly unlikely that these regulations will be finalized and implemented in the near future. We believe it is premature to revise the FDA 3500A form to include these data elements until the underlying regulations and associated guidance documents are finalized.

2. *Comment on the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used*

With regard to the estimates used for industry reporting to CBER and CDER, we believe that the figures include only the time required to complete the form, and do not take into account the associated costs and resources required to implement the proposed changes to the Form FDA 3500A. These costs include not only the expense involved with modifying databases to include new fields, and reprogramming and revalidating the associated computer-generated forms, but also the necessary changes in company procedures related to collecting the newly required information, and the associated documentation and training.

3. *Ways to enhance the quality, utility, and clarity of the information to be collected*

As noted above, if the Agency does make the proposed revisions to the Form FDA 3500A, FDA should update the instructions for completing the Form FDA 3500A, and issue them in conjunction with the final revised form. This will clarify the Agency's intentions regarding use of the new fields, and greatly enhance the consistency of data provided to the Agency from multiple sources.

4. *Ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology*

For years, the Agency has been working with industry to implement electronic submission of adverse event reports using internationally accepted ICH standards for content and format. Implementation of this initiative is well underway, saving the agency considerable expense associated with manually entering these reports into the AERS database, along with the added benefit of having the data available for review in a much more timely manner. As companies move to submitting all of their reports to FDA electronically, they will use paper FDA 3500A forms only as a back-up for the rare occasions when networks or servers are inoperable. The amount of financial and human resources required to implement the proposed changes to the FDA 3500A for what is essentially an emergency back-up use is not an efficient use of these resources. Therefore, as noted above, we recommend that the Agency grant waivers to

companies who use electronic submission as their primary means of reporting to FDA, even when paper forms are required in an emergency.

Thank you for your consideration of these comments.

Sincerely,

A handwritten signature in black ink, appearing to read 'E. Pattishall', written in a cursive style.

Edward N. Pattishall, MD, MPH
Vice President
Global Clinical Safety & Pharmacovigilance